REMARKS

Claims 13-19 are pending in the application. Claims 1-5, 7, and 9-12 have been cancelled without prejudice. The subject matter of these claims has been rewritten as new claims 13-19. No new matter is incorporated into new claims 13-19; support for the subject matter of each new claim is found at least in the specification at page 4, lines 5-6 and 28-29, page 8, lines 24-25; and in claims 1-12 as originally filed.

The Examiner's objection and rejections are addressed in the order they appear in Paper No. 12.

I. Objection to Specification.

At page 2 of Paper No. 12, the Examiner has objected to the specification and requested that the applicants update the status and relationship of the priority documents. The applicants have amended the specification accordingly. This amendment does not constitute new matter, as the subject matter of the amendment is supported in the Preliminary Amendment, filed simultaneously with the patent application on May 3, 2001.

Accordingly, it is respectfully requested that the Examiner's objection be reconsidered and withdrawn.

II. Priority Under 35 U.S.C. § 119.

At numbered paragraph 2 of Paper No. 12, the Examiner has asserted that the applicants are not entitled to claim the benefit of foreign priority to United Kingdom Application No. 9414966.3, filed July 26, 1994 under 35 U.S.C. § 119 because the claims are allegedly not supported by the disclosure of the United Kingdom application. Therefore, according to the Examiner, the priority date of the claims is July 24, 1995, the date of filing of the International Patent Application to which this U.S. application claims priority.

The applicants do not concede the accuracy of the Examiner's statement. However, as none of the prior art references cited in the present Office Action has a disclosure date under § 102 subsequent to July 26, 1994 but prior to July 24, 1995, the Examiner's assertion is considered moot at present. Accordingly, in order to facilitate the prosecution of the

application, the applicants will not address the Examiner's comments at this time. However, the applicants reserve the right to address the issue should the Examiner cite prior art having a § 102 date subsequent to July 26, 1994, the filing of the United Kingdom application.

III. Rejections Under 35 U.S.C. § 103(a).

The Examiner has maintained the rejections of claims 1-5, 7, and 9-12 under 35 U.S.C. §103(a), asserting that the claims are unpatentable over three permutations of the following references: (i) U.S. Patent No. 5,482,706 of Igari, et al. ("Igari"); (ii) U.S. Patent No. 5,589,453 of Greve, et al. ("Greve"); (iii) U.S. Patent No. 5,730,983 of Wenger, et al. ("Wenger"); (iv) U.S. Patent No. 5,422,907 of Gwaltney, et al. ("Gwaltney"); (v) U.S. Patent No. 5,690,954 of Illum ("Illum '954"); (vi) U.S. Patent No. 5,707,644 of Illum ("Illum '644"); and (vii) Kublik, et al., *Eur. J. Pharm. Biopharm.* 39:192-196, 1993 ("Kublik"). Relying on these references, the Examiner has asserted three rejections under 35 U.S.C. § 103:

- claims 1-5, 7, and 9-12 are unpatentable over the combination of Igari and Greve, taken in view of Wenger, Gwaltney, Illum '954, Illum '644, and Kublik;

- claims 1-5, 7, and 9-12 are unpatentable over Igari alone taken in view of Wenger, Gwaltney, Illum '954, Illum '644, and Kublik; and

- claims 1-5, 7, and 9-12 are unpatentable over Greve alone taken in view of Wenger, Gwaltney, Illum '954, Illum '644, and Kublik. The applicants respectfully traverse each of these rejections for the reasons set forth below, and request that they not be applied to new claims 13-19.

Igari and Greve

The two primary references as set forth by the Examiner as basis of each of the three § 103 rejections are Igari and Greve. Igari teaches a transmucosal therapeutic composition that is a physiologically active peptide or protein and a cytidine nucleotide derivative and which is designed to facilitate systemic delivery of the cytidine nucleotide. Igari teaches that the physiologically active peptide or protein for use in the Igari composition can be a cell adhesion factor, such as laminin and Intracellular Adhesion Molecule 1 (ICAM-1). Igari teaches that the

selected physiologically active peptide or protein and the cytidine nucleotide derivative may be dispersed into a pharmaceutically acceptable base or vehicle. Igari teaches that this base is copolymers of polycarboxylic acids, carboxylic anhydrides, polyvinyl acetate, polyvinyl alcohol, polyvinyl pyrrolidone, hydroxymethyl cellulose, hydroxypropyl cellulose, chitosan, collagen, sodium alginate, gelatin, hyaluranoic acid, polyglycerin fatty acid esters, or sucrose fatty acid esters. *See* col. 9, lines 8-39. Igari generally teaches that the base or vehicle may be molded into suppositories, films, or microspheres. Moreover, Igari does not teach or suggest a liquid formulation comprising chitosan, nor does it specifically teach the preparation of microspheres of one of starch, chitosan, gelatin, hyaluronic acid, alginate, or gellan, into which ICAM-1 has been incorporated. The Examiner notes that Igari does not teach the ability of ICAM-1 to inhibit rhinovirus infections.

Greve discloses a water soluble preparation of the human rhinovirus major receptor that exhibits the property of binding to human rhinovirus capsids, thereby reducing the infectivity of the virus. The preparation is composed of detergent-complexed glycoproteins that are isolated from animal cells but express the human rhinovirus major receptor. Greve states in the abstract that the human rhinovirus receptor protein has been determined to be ICAM-1, although no primary amino acid sequences are disclosed in Greve. Greve does not teach that the preparation can be formulated into any type of pharmaceutical composition, nor do the Examples in Greve demonstrate any *in vivo* use of the preparation. All examples are conducted *in vitro* using, for example, cell culture suspensions. The Examiner himself concedes that Greve does not disclose a composition including a bioadhesive (such as the liquid formulation of chitosan or the microspheres as recited in the claims).

Wenger

Wenger teaches a use agents which prevent or exhibit cellular adhesion, such as ICAM-1, in the treatment of asthma. Wenger teaches that the anti-asthma agents may be administered to the lungs by any suitable means, including nasal spray or swab and injection, but emphasizes that is preferred to administer the agent by oral inhalation, oral spray or oral aerosol. The Wenger composition prevents the migration of eosinophils to the lung. Thus, it is designed to deliver ICAM-1 to lung endothelia, not to the nasal cavity. To administer the agents, Wenger

teaches that the agents can be formulated into a "pharmaceutically useful composition" by admixing the agent with a pharmaceutically acceptable carrier vehicle. No specific teaching of carrier vehicles is provided. Wenger teaches that the pharmaceutically useful compositions may be achieved by entrapping the ICAM-1 in colloidal drug delivery systems such as liposomes, albumin microspheres, micoremulsions, nanoparticles, or nanocapsules. Wenger does not teach use of ICAM-1 and a liquid formulation that includes chitosan, nor does it specifically teach or suggest that microspheres can be formulated from chitosan, gelatin, starch, hyaluronic acid, alginate, and gellan.

Gwaltney

Gwaltney discloses a composition comprising anti-viral agents and an anti-inflammatory compound to be administered to a patient infected with a cold virus. The anti-inflammatory compound is intended to be taken up systemically. Gwaltney also discloses that the composition may contain substances which prevent the attachment of rhinovirus to nasal cells such as anti-ICAM-1 antibody and synthetic ICAM-1. However, Gwaltney does not teach incorporation or encapsulation of the antiviral agent and anti-inflammatory compound into a microsphere, nor does Gwaltney teach use of a liquid formulation including chitosan.

Illum '954 and Illum '644

Illum '954 and Illum '644 (collectively, "the Illum references") teach use of drug delivery composition containing microspheres comprising starch, gelatin, dextran, collagen, and gellan gum for use in the administration of drugs to a human patient (Illum '644). Neither of the Illum references discloses use of a composition containing ICAM-1. Illum '664 and '954 is designed to deliver drugs systemically by the nasal route, not to deliver to the nasal cavity.

Kublik

Kublik provides a general teaching concerning the use of nasal applications of drug compositions for systemic drug delivery. Kublik provides a rheological characterization of solutions for nasal administration containing Gelrite™ (gellan gum) and hydroxymethylcellulose. However, Kublik teaches that the rheological properties of a given solution do not necessarily bear a relationship to the viscosity and/or bioavailability of nasally

administered polymer solutions. Additionally, Kublik does not disclose compositions containing chitosan in any form nor does it disclose use of a bioadhesive that is a microsphere that includes chitosan, gelatin, starch, hyaluronic acid, alginate, and gellan, or compositions containing ICAM-1.

The Invention

The invention of this application is a drug delivery composition for nasal administration that includes (i) ICAM-1 and (ii) a liquid formulation comprising chitosan (claims 13-16, and 19) or a plurality of microspheres including a starch, chitosan, gelatin, hyaluronic acid, alginate or gellan (claims 17-18, and 19). The composition is adapted to deliver to the nasal cavity an antivirally effective amount of ICAM-1. If the composition contains a liquid formulation that includes chitosan, the composition contains ICAM-1 in a concentration between 0.02 and 2.0% by weight per volume. If the composition contains microspheres including a starch, chitosan, gelatin, hyaluronic acid, alginate or gellan, the ICAM-1 is present in an amount of between about 0.1 and 50% by weight of the microspheres. The invention is also a method of delivering ICAM-1 to the nasal cavity that includes administering the compositions.

The compositions of the invention are useful to effectively deliver amounts of anti-viral material to the cells or lining of the nasal cavity. Lack of *in vivo* efficacy when an active agent is delivered via the nasal route is known to occur due to the nasal mucus clearance process which facilitates removal of the administered agent from the mucosal surface before it can be effective. The prior art has attempted to address this problem with respect to <u>systemic</u> delivery of active agents (i.e., those active agents which are intended to pass through the nasal mucosa and into the bloodstream).

In contrast, the present invention addresses a different problem, namely, the difficulty in administering an active agent to the nasal cavity. The effectiveness of the composition is due to the delay in mucociliarly clearance of the ICAM-1 by use of the unique components of the composition, including the bioadhesive (i.e., the chitosan formulation or the microspheres).

None of the Combinations Suggested By the Examiner Renders the Invention Obvious

In order for the Examiner to establish that any of the three stated combinations of the above references renders the invention obvious, the Examiner must demonstrate, with respect to each combination: (i) that each teaches or suggests each element of the claims; (ii) that there would have been motivation in the art to one of ordinary skill to mix the combination suggested by the Examiner; and (iii) that the person of skill in the art would have had a reasonable expectation that, in making such combination suggested by the Examiner, he would obtain successful results. No such showing has been made.

The Examiner has failed to make a *prima facie* case that the invention as described in the claims is rendered obvious by any of the three combinations of references. First, none of the combinations suggested by the Examiner teaches or suggests each element of the invention. Specifically, each of the three combinations proposed by the Examiner omits elements of the invention as claimed: (1) a liquid formulation comprising chitosan containing ICAM-1 or microspheres prepared from the recited materials, (2) a composition adapted to deliver to the nasal cavity an antiviral effective amount of ICAM-1, and (3) ICAM-1 in a concentration of between about 0.02 and 20% by weight per volume.

None of the references teaches or suggests that the composition should include a liquid formulation comprising chitosan. The base materials in Igari are taught as being formed into suppositories, films or microspheres. No liquid formulation is taught. Greve, the other primary reference set forth by the Examiner does not teach any suitable base, excipient, or carrier substance. In fact, Greve does not even teach or suggest that the ICAM-1 disclosed therein can be formulated into any type of pharmaceutical composition. The addition of the teachings of Gwaltney, the Illum references, and Kublik does not remedy this deficiency. Neither Gwaltney nor the Illum references teaches incorporation of any active agent into a liquid formulation that comprises chitosan. Kublik teaches only solutions that contain gellan gum and hydroxymethylcellulose, but provides no teaching or suggestion to use chitosan.

None of the references teaches microspheres comprising starch, chitosan, gelatin, hyaluronic acid, alginate or gellan and ICAM-1. Neither Igari, Greve, Kublik, or Gwaltney

discusses microspheres in any context. Wenger discloses use of albumin microspheres only, and the microsphere preparations in the Illum references are used in compositions for systemic delivery of drugs.

Additionally, none of the references which make up each of the proposed combinations by the Examiner teach or suggest a drug delivery composition for nasal administration that is adapted to deliver to the nasal cavity an antiviral effective amount of ICAM-1. As discussed above, Greve makes no teaching of any type of pharmaceutical composition. Igari teaches a composition for systemic delivery of a cytidine nucleotide or nucleotide derivative. The Wenger composition is designed to accomplish the prevention of migration of eosinophils to the lung tissue; thus it is designed to deliver ICAM-1 to the lung endothelia through the nasal route, not, to the nasal cavity, as is the present invention. The Gwaltney composition is designed for the systemic administration of antiviral agents and anti-inflammatory compounds. As an aside, Gwaltney teaches that the composition may contain a substance which prevents the attachment of rhino virus to nasal cells, such as ICAM-1, but, as can be seen from the remaining Gwaltney disclosure, the composition itself is directed to the systemic administration of antiviral agents and anti-inflammatory compounds. Similarly, all of the active agents disclosed in the Illum references are those which require systemic administration either through the nasal route, as taught in Illum, or through other means. Finally, Kublik specifically and expressly teaches that the information provided therein relates to the use of nasal applications of drug compositions for systemic delivery.

The Examiner concedes that none of the references teaches a composition having the recited amount of chitosan. Therefore, because each combination does not teach or suggest all elements of the invention, no *prima facie* case of obviousness has been made.

Moreover, even assuming that any one of the proposed combinations did meet each element of the invention as claimed, a person of skill in the art would have had no motivation in the art to make any of the combinations suggested by the Examiner, nor would he have had a reasonable expectation that such combination would give rise to a successful composition for nasal administration of ICAM-1 to the nasal cavity. Greve makes no disclosure of any pharmaceutical composition or *in vivo* pharmaceutical use of ICAM-1. None of the remaining

references cited by the Examiner address the difficulty of preparing a composition that allows for the administration of an active agent to the nasal cavity. Gwaltney, the Illum references, and Kublik each teach compositions that are adapted for transport of the selected active agent via the nasal route into the bloodstream. Wenger is expressly designed to administer the ICAM-1-containing composition to the endothelial cells of the lung, via any feasible administration route, including oral or nasal routes. Accordingly, a person seeking to prepare a composition which is adapted to deliver an antivirally effective amount of ICAM-1 to the nasal cavity would not rely upon, or combine teachings of, references directed to compositions which facilitate systemic administration of a drug or active agent. Further, given these teachings, it is unlikely that a person of skill would have had a reasonable expectation of success.

Conclusion

In view of the foregoing, it is respectfully submitted that each of the Examiner's objections and rejections has been addressed or overcome. Accordingly, reconsideration and allowance of claims 13-19 at the earliest opportunity is earnestly solicited.

Respectfully submitted,

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